LHRH - ANTAGONISTS IN THE TREATMENT OF FERTILITY DISORDERS

Cross references to Related Applications

This application is based on provisional application serial No. 60/011,282 filed February 7, 1996, the content of which is incorporated herein by reference.

Field of the Invention

The field of invention is directed to the use of LHRH-antagonists to treat male and female fertility disorders.

Background of the Invention

The reasons for unsuccessful attempts to establish pregnancy can be attributed equally to male and female fertility disorders. Today many different assisted reproduction techniques are available. These techniques are used to induce multiple and synchronous follicular growth and thereby obtain fertilizable oocytes.

The current standard treatment is to induce multiple follicular development by administering high doses of HMG (Human Menopausal Gonadotropin). This results in ovarian hyperstimulation. Upon reaching a suitable degree of oocyte maturation using these techniques, ovulation is induced by the administration of HCG (Human Chorion-Gonadotropin) in order to obtain a sufficient number of oocytes. During this time, the clinic-infrastructure preparation can begin. Preparation includes recovery of oocytes by abdominal or transvaginal puncture, intracorporal or extracorporal fertilization of oocytes by different techniques and embryo replacement into the uterus. Routinely, beginning pregnancy is supported by additional administrations of HCG or progesterone. Today this

treatment is applied to clinical conditions of male and female infertility.

Complications that are frequently observed during the hyperstimulation procedure are:

A: premature surges of luteinizing hormone (LH) at a premature maturation state with a rupture of the follicles that induced a subsequent cancellation of the treatment occurring in about 25% of the patients; and B: ovarian hyperstimulation syndromes induced by exogenous gonadotropins which in severe cases require hospitalization and are life-threatening.

In order to avoid premature LH-surges, today LHRH-agonists are used as a comedication. By continued administration of these drugs, a complete suppression of endogenous gonadotropins is achieved by desensitization of pituitary cells and down-regulation of their receptors. Subsequently, the gonadotropin levels can be controlled by exogenous injection and the pituitary is refractory to the stimulation of LH-release by increasing levels of estradiol. Disadvantages are 1) a long treatment period until the suppression and down-regulation occur; 2) estrogen withdrawal symptoms; 3) disturbance of the normal menstrual cycle; 4) the need for frequent hormone determinations in order to evaluate the time of onset of suppression; and 5) high dose HMG treatment is needed for ovarian stimulation.

The pathogenesis of hyperstimulation syndrome is not completely understood, but is thought to be associated with the use of HCG for ovulation induction and luteal phase support.

One recent approach involves the use of the LHRH antagonist Cetrorelix (INN). In first clinical trials, short term treatment with Cetrorelix resulted in a complete avoidance of premature LH surges during stimulated cycles and the need for HMG. Due to the immediate

suppression of gonadotropins by this antagonist, the unwanted stimulatory phase and also the withdrawal of estrogen produced by the agonists was avoided. The duration of treatment was also significantly shortened. In addition, it was shown that a single injection of an antagonist, given in the mid-follicular phase, would adequately suppress premature LH surges.

SUMMARY OF THE INVENTION

Despite the improvements described above, these treatment modalities suffered the drawback of treating the patients with the highest possible dose of exogenous gonadotropins to hyperstimulate multiple follicular development which results in some severe adverse events.

The current invention reduces the severe adverse events, improves patient compliance and reduces costs. Recent data obtained with Cetrorelix also demonstrates additional surprising new advantages for the treatment of male and female infertility.

In animal experiments and clinical studies with Cetrorelix, it was possible to induce an arrest of the normal, unstimulated follicular growth by multiple or single injections. These effects were observed with extremely low dosage levels. These low dosage levels present new possibilities for manipulating the time of ovulation during a normal, not exogenous gonadotropin-stimulated cycle, without affecting the viability of the growing follicle. In case of inadequate follicular growth related to treatment with LHRH-antagonists, low dose and short term administration of gonadotrophin or other trophic compounds will compensate for these effects. Subsequently, by stopping the LHRH-antagonist treatment, it is possible to let the normal ovulation occur or to induce ovulation by exogenous manipulation, if necessary. Ovulation induction was induced by

the administration of standard HCG or by administration of LHRH and/or LHRH agonistic analogs.

These described treatment alternatives are a departure from existing protocols, since they are possible only if preceded by treatment for LH-surge-control with an LHRH-antagonist. In animal and clinical studies with Cetrorelix it was shown that the responsiveness of the pituitary to LHRH or agonistic analogs is preserved under these conditions of treatment. Without this treatment, the pituitary cannot respond after agonistic pretreatment for LH-surge control due to receptor down-regulation. In addition, the possible use of ovulation inducing agents other than HCG results in a reduced incidence of ovarian hyperstimulation syndrome.

On the basis of the described results, for the first time it is possible to use normal, non-gonadotropin-stimulated cycles for assisted reproduction techniques, including sperm injections, by determining the time of ovulation by the duration and dose of Cetrorelix given. Especially in conjunction with the method of ICSI (Intra-Cytoplasmatic-Sperm-Injection) this antagonist-dependent treatment modality facilitates the inclusion of in-(sub-)fertile males into this kind of fertility treatment. Due to the direct injection of male gametes capable for fertilization, this method has a high success rate and hence, allows the harvest of only one follicle for fertilization. In addition, the use of LHRH-antagonists like Cetrorelix in the described manner relieves the patient from severe ovarian hyperstimulation and significantly reduces the costs of a treatment cycle.

LHRH-antagonists of the invention can be used in combination with assisted reproduction techniques, especially the extracorporal fertilization, e.g. the in-vitro fertilization and the sperm injection techniques.

Compounds with the desired LHRH-antagonistic activity include a LHRH-analog such as Ganirelix, Antarelix, Antide, Azaline B, Ramorelix, A-76154, Nal-Glu, 88-88, in particular Cetrorelix or a structure-truncated peptide with LHRH-antagonistic activity or a peptideomimetic with LHRH-antagonistic activity, for example D-23980 and D-24824, or a bicyclic (1-4. 4-10) LHRH analog with antagonistic activity.

LHRH-antagonists of the invention can be subcutaneously administered in dosage amounts of about 0.001-0.2 mg/kg.

Both dosing schedules demonstrate the prevention of any premature LH surge. After both posologies good fertilization rates have been obtained with good follicle and oocytes quality. Pregnancy rates are good after both treatments. To date, a total of 44 healthy babies are born following both treatments.

The single dose regimen requires only one single injection of 3 ml. This has to be regarded as being convenient for the patient. So far, duration of effect to prevent a premature LH surge is up to 6.5 days. After 3 days, monitoring of hormones is advisable in order to apply a second injection in case of a low responder to HMG with prolonged administration of HMG, and if an increase of LH values is seen.

The multiple dose schedule requires daily injections of 1 ml for 3 to 7 days, sometimes up to 10 or 14 days. This is not as convenient as a single or dual injection. On the other hand, regular monitoring of the hormones is not required and the application of HCG could even be extended if required in rare cases.

In summary, from a medical point of view, both treatments show comparable efficacy, safety and practicability, therefore each gynecologist should have the possibility to decide upon the dosing schedule with respect

to the situation observed in each single patient.

The results of a phase II clinical trial are shown in Table I. A total of 235 patients were treated.

No premature LH surge was seen in any patient undergoing COS/ART treated with either multiple doses of 0.25 mg or higher or a single dose of 3 mg or higher. During multiple dosing, the mean days of Cetrorelix application is 6 days. 25 babies were born by the end of May 1996 (7 following multiple doses; 18 following single/dual doses).

Table I

Cetrorelix Development Controlled Ovarian Stimulation (COS/ART)				
	Subj. Nos.	Phase	Dose/Day (mg)	Posology (days)
	14	II/proof concept	3	3-10
	19	II/proof concept	1	3-10
	11	II/proof concept	0.5	3-10
	32 30 (28)	II/ dose finding/ minimal effective dose	0.5 0.25 min. effect. dose 0.10 no effect. dose	3-7/14
	21	II/proof concept	5	1 or 2
	18	II/proof concept	3	1 or 2
	32 30	II/dose finding/ minimal effective dose	3 min. effective dose 2 no effect. Dose	1 1
SUM Phase II	235 finished		71 pregnancies (30%) 16 pregnancies (ongoing)	44 healthy children

The main advantages in controlled ovarian stimulation (COS/ART) with Cetrorelix are:

1. New therapeutic principle

    a) Prevention of premature LH-surges

    b) Uniform and continuous follicular synchronization

    c) Uniform and continuous estradiol development

    d) Very low LH-values for optimal follicular development

2. Short term treatment of 3 to 7 days to max 14 days

    a) Short-term exposure during follicular development

    b) Low medication exposure during follicular development

3. No flare-up but immediate hormonal response

4. No pretreatment for 14 to 21 days before start of HMG needed

5. Fits well into normal menstrual cycle with

    a) No modification of physiological menstrual cycle pattern or

    b) No hormonal withdrawal syndromes before stimulation

6. No or only ultrashort-term residual effects after ovulation induction

7. No residual effects during and following embryo transfer

8. No ovarian cyst formation before start of stimulation

9. Reduction of HMG.

Table II (flow chart) shows an example on a typical treatment start and duration of HMG and Cetrorelix in patients to undergo controlled ovarian superovulation for ART.

Summary of assessments Table II (Flow-chart)

PERIOD:		hMG[2] PERIOD d1→ until day of hCG:				hCG[4] apply if:	POST hMG PERIOD			
Treatment / Investigations				Cetrorelix		lead follicle: ≥ 20 mm ϕ or E_2 ≥ 1,200 pg/ml				
Parameters:	pre	hMG day 1[1] Cycle day 2 or 3	hMG days d2 - d5	hMG day d6	hMG day[2] d7 until the day of hCG	cancel, if: ≥12 foll. ≥15 mmϕ or E_2 ≥ 4,000 pg/ml (≥ 14,684 pmol/l)	OPU	ET	6 - 8 days after ET	Final Docum.: Day 20-25 after ET
Screening data	X									
End of Trial Form										X[6]
Cetrorelix 0.25 mg s.c. daily				X	X	X				
hMG inj. (2/3/4+)		X[1] 2 Amp	X 2 Amp	X 2+++ Amp	X[2] 2+++ Amp	X[2] 2+++ Amp				
→ hCG 10,000 IU i.m. injection						X[3]				
Ultrasound (USS)	X	X		(X) optional	(X) optional	X	X			X
Hormones: (hCG) LH, FSH, E_2, P	X	X[1]		X	X daily	X[7] 2-times: morning+ just before hCG	X	X	X	X
Lab (Hemat., clin. chem.)	X			X			X		X	
Luteal phase support → hCG or Progesterone								X[5]	X[5]	
Tolerability / AE's	X	<. .....at every visit .... >								

Pregnancy and Baby follow up

Follow-up: replacement cycles

X^1 = 1st day **(d 1)** of hMG injection: **after confirmation (verified in the morning) of**, menstrual bleeding; no pregnancy hCG → neg. (≤ 10 IU/l); P ≤ 1ng/ml (≤ 3.81 nmol/l);FSH ≤ 10 IU/l ; no ovarian cyst (≥ 2 cm ϕ producing E_2 ≥ 50 pg/ml (≥ 185 pmol/l)). **d1 of hMG = day 2 or 3 of menstrual cycle !**

X^2 = last day of hMG administration depends on follicle maturation (see X^3).

X^3 = day of injection of 10.000 IU hCG: as soon as at least 1 follicle with a mean diameter of 20 mm, measured by ultrasound (USS) **or** E_2 ≥ 1 200 pg/ml (≥4 405 pmol/l), is observed.

X^4 = **CAVE:** In case of > 12 follicles ≥ 15 mm ϕ **or** E_2 ≥ 4 000 pg/ml (≥ 14 684 pmol/l) during stimulation period → **no hCG injection ! → Cycle cancellation !**

X^5 = **Luteal phase support according to centre's rule: Either** injections of hCG according to centre's rule **or** vagin application of Progesterone (e.g. 3x 200 mg/day) will be given accord. to centre's rule.!

X^6 = Must always be documented in any case of any premature study termination (e.g. in case of any Drop out) .

X^7 = Blood samples for hormone determination on the day of hCG will be withdrawn 2 times (morning and just before hCG application) at hospital or outsite.

Ultrasound (USS): (X) will be undertaken according to centre's rule between day 6 of hMG until the day of hCG ! USS has to be performed on the day of HCG!

Example

238 patients were treated with Cetrorelix by subcutaneous injection of Cetrorelix Acetat-Lyophilisat.

134 patients were treated with multiple doses and 104 patients with single or dual doses. The multiple doses are 0.25 mg/day or higher. The single dose was 3 mg or higher. No premature LH surge was seen in any patient undergoing controlled ovarian superovulation for assisted reproduction technology (COS/ART) treated with these dosages. Multiple doses were applied for 3 to a maximum of 10 days dependent on follicular development.

As a result 71 pregnancies were obtained = 30.0%

38 of 134 following the multiple does regimen = 28.4%

33 of 104 following the single/dual dosage regimen = 31.7%

Following treatment 44 babies were born that means 15 following multiple does and 29 following single/dual does. 16 pregnancies are still ongoing. Figure 1 shows this in particular

Figure 1 shows an absolute prevention of any premature LH surge. Furthermore, FSH secretion is maintained at a natural level and therefore the individual estrogen development is not affected.

WHAT IS CLAIMED IS:

1. In the method of treating infertility disorders by administering an LH-RH antagonist and inducing follicle growth by administration of exogenous gonadotropin wherein the improvement comprises administering an amount of LH-RH antagonist sufficient to selectively suppress endogenous LH but not FSH secretion which is maintained at a natural level thereby not affecting individual estrogen development.

2. The method of treating infertility disorders by administering a LH-RH antagonist and inducing follicle growth by administration of exogenous gonadotropic according to claim 1 wherein the improvement further comprises using Cetrorelix as the antagonist.

3. The method according to claim 2 wherein the improvement further comprises stimulating follicle growth with substances other than exogenous gonadotropins.

4. The method according to claim 2 wherein the improvement further comprises maintaining the follicle development by endogenous gonadotropins after inhibition of the action of natural LH caused by the LH-RH antagonist preferably, Cetrorelix.

5. The method according to claim 2 wherein the improvement further comprises administering the Cetrorelix subcutaneously in an amount in the range of 0.1 to 0.5 mg of Cetrorelix/day during multiple

dosing posology.

6.. The method according to claim 1 wherein the LH-RH antagonist is given as a single or dual subcutaneous dose in the range of 1 mg to 10 mg, preferably 2 mg - 6 mg.

7. The method of controlled ovarian stimulation in which the LH-RH antagonist preferably Cetrorelix is applied according to claim 6 starting on cycle day 6 to 10 and ovulation can be induced between day 9-16 of the menstruation cycle.

8. The method according to claim 7 wherein native LHRH or a LHRH agonist are given to avoid luteal phase stimulation in preventing the negative effects of HCG during the luteal phase.

9. The method according to claim 7 wherein rec. LH, native LHRH or LHRH agonist are given to avoid hyperstimulation syndrome.

10. The method of controlled ovarian stimulation comprising administering Cetrorelix to a subject starting on cycle day 1 to 10, preferably on day 4 to 8 and inducing ovulation between day 9 and 20 of the menstruation cycle.

11. The method according to claim 10 whereas the ovulation is induced by rec. LH.

12. The method according to claim 10 whereas the ovulation is induced by native LHRH.

13. The method according to claim 10 whereas the ovulation is induced by a LHRH agonist.

14. The method according to claim 10 whereas the ovulation is induced by HCG.

ABSTRACT

A method of treating infertility disorders by 1) administering an LH-RH antagonist, preferably Cetrorelix, in amounts to selectively suppress endogenous LH but not FSH secretion and 2) inducing follicle growth by administration of exogenous gonadotropin. The selective suppression OF LH allows FSH secretion to be at natural levelS thereby not affecting individual estrogen development. The LH-RH antagonist can be given as a single or dual subcutaneous dose in the range of 1 mg to 10 mg, preferably 2 mg - 6 mg. In multiple dosing posology, LH-RH antagonist can be administered subcutaneously in an amount in the range of 0.1 to 0.5 mg of LH-RH antagonist/day . LH-RH antagonist is applied starting cycle day 1 to 10, preferably on day 4 to 8, and ovulation can be induced between day 9 and 20 of the menstruation cycle by administering rec. LH, native LH-RH, LH-RH agonist or by HCG. In addition rec. LH, native LH-RH or LH-RH agonist can be given to avoid hyperstimulation syndrome and native LH-RH or a LH-RH agonist can be administered to avoid luteal phase stimulation by neutralizing the negative effects of HCG.

FOR UTILITY/DESIGN
CIP/PCT NATIONAL/PLANT
ORIGINAL/SUBSTITUTE/SUPPLEMENTAL
DECLARATIONS

RULE 63 (37 C.F.R. 1.63) DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CUSHMAN FORM

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED LHRH-ANTAGONISTS IN THE TREATMENT OF FERTILITY DISORDERS

the specification of which (CHECK applicable BOX(ES))

X → ☒ was filed on January 22, 1997 as U.S. Application No 08/786,937

BOX(ES) ☐ was filed as PCT International Application No. PCT/ / on

→→ and (if applicable to U.S. or PCT application) was amended on

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S) Number	Country	Day/MONTH/Year Filed	Date first Laid-open or Published	Date Patented or Granted	Priority Claimed Yes	No
					☐	☐
					☐	☐
					☐	☐
					☐	☐

I hereby claim domestic priority benefit under 35 U.S.C. 119/120/365 of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application:

PRIOR U.S. PROVISIONAL, NONPROVISIONAL AND/OR PCT APPLICATION(S) Application No. (series code/serial no.)	Day/MONTH/Year Filed	Status pending, abandoned, patented	Priority Claimed Yes	No
60/011,282	07 FEB 1996	pending	☒	☐
			☐	☐
			☐	☐
			☐	☐

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint Cushman Darby & Cushman Intellectual Property Group of Pillsbury Madison & Sutro LLP, 1100 New York Avenue, N.W., Ninth Floor, East Tower, Washington, D.C. 20005-3918, telephone number (202) 861-3000 (to whom all communications are to be directed), and the below-named persons (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete names/numbers below of persons no longer with their firm and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or a below attorney in writing to the contrary.

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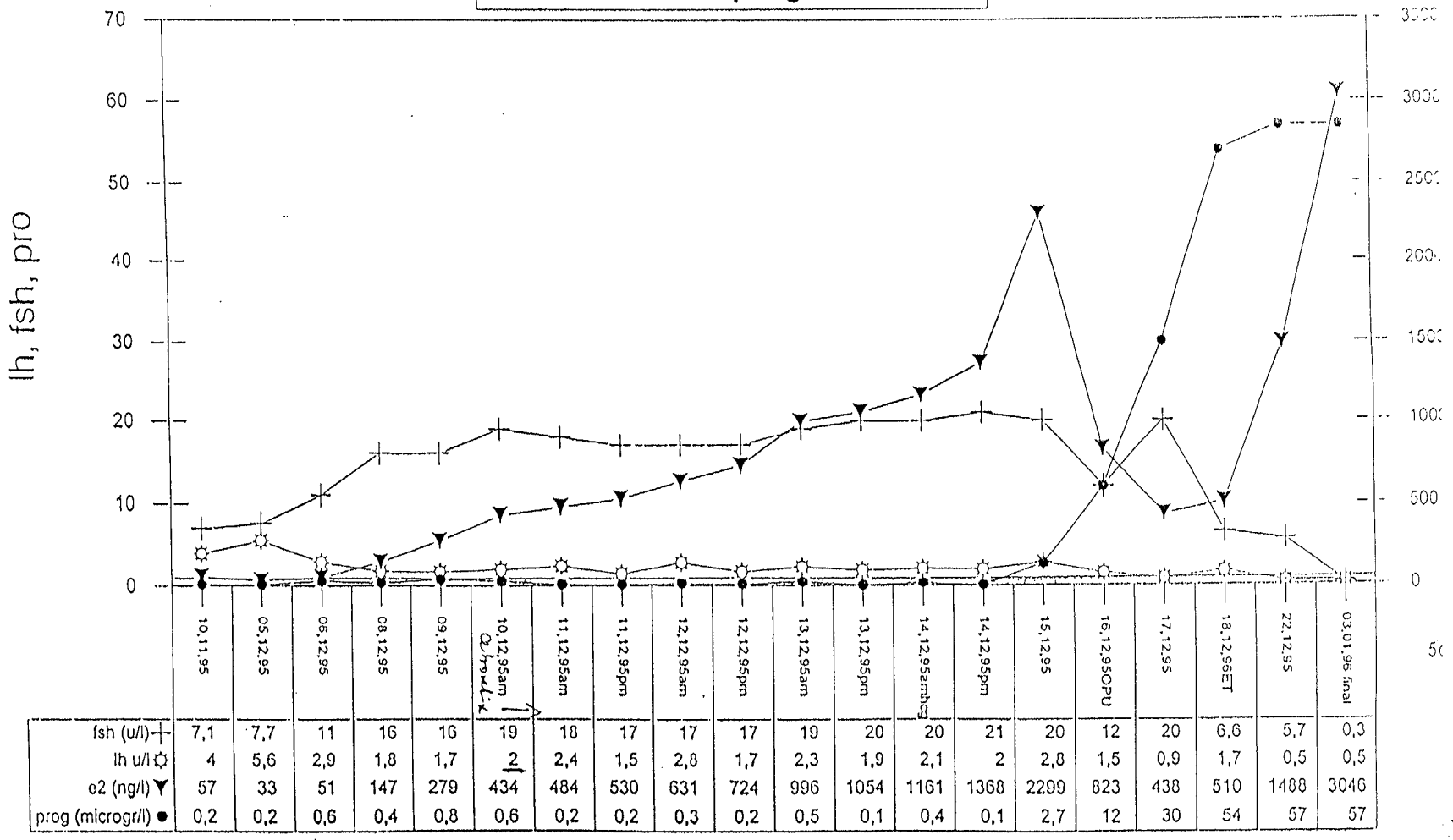
Figure 1

Cetrorelix Study

- hormone levels -

Pat. No. 2L/07 pregnant



	10.11.95	05.12.95	06.12.95	08.12.95	09.12.95	10.12.95am Q/hmdix	11.12.95am	11.12.95pm	12.12.95am	12.12.95pm	13.12.95am	13.12.95pm	14.12.95ambg	14.12.95pm	15.12.95	16.12.95OPU	17.12.95	18.12.95ET	22.12.95	03.01.96 final
fsh (u/l) ┼	7,1	7,7	11	16	16	19	18	17	17	17	19	20	20	21	20	12	20	6,6	5,7	0,3
lh u/l ☼	4	5,6	2,9	1,8	1,7	2	2,4	1,5	2,8	1,7	2,3	1,9	2,1	2	2,8	1,5	0,9	1,7	0,5	0,5
e2 (ng/l) ▼	57	33	51	147	279	434	484	530	631	724	996	1054	1161	1368	2299	823	438	510	1488	3046
prog (microgr/l) ●	0,2	0,2	0,6	0,4	0,8	0,6	0,2	0,2	0,3	0,2	0,5	0,1	0,4	0,1	2,7	12	30	54	57	57

08/28692

08/786937

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING APPLICATION
Under Rule 53(a), (b)(l) & (d)(l)
(No Filing Fee or Oath/Declaration)
(Do NOT use for Provisional or PCT Applications)
Use for Design or Utility Applications

PATENT APPLICATION

RULE 53(d) NO DECLARATION

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Atty. Dkt. 235299 (M#) | 960018PH/De (Client Ref)

Date: January 22, 1997

Sir:

1. This is a Request for filing a new Patent Application(☒ Design ☐ Utility) entitled:

2. (Complete) Title: LHRH-ANTAGONISTS IN THE TREATMENT OF FERTILITY DISORDERS

without a filing fee or Oath/Declaration but for which is enclosed the following:

3. ☒ Abstract 1 page(s).

4. 13 Pages of Specification (only spec. and claims); 5. ☐ Specification in non-English language

6. 14 Numbered claim(s); and

7. ☒ Drawings: 1 sheet(s) per set: ☒ 1 set informal; 8. ☐ formal of size: ☐ A4 ☐ 11"

9. **DOMESTIC/INTERNATIONAL** priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international application(s):

Application No.	Filing Date	Application No.	Filing Date
(1) 60/011,282	Feb 7, 1996	(2)	
(3)		(4)	
(5)		(6)	

10. **FOREIGN** priority is claimed under 35 USC 119(a)-(d)/365(b) based on filing in _____

Application No.	Filing Date	Application No.	Filing Date
(1)		(2)	
(3)		(4)	
(5)		(6)	

11. _____ (No.) Certified copy (copies): ☐ attached; ☐ previously filed (date) _____
in U.S. Application No. / filed on _____

12. ☐ **Amend the specification** by inserting before the first line - This is a ☐ Continuation-in-Part ☐ Divisional ☐ Continuation ☐ Substitute Application (MPEP 201.09) of:

12(a) ☐ National Appln. No. / filed .- - (M#)
12(b) ☐ International Appln. No. PCT/ filed _____ which designated the U.S. - -

13. ☐ See top of first page re continuing appln (X box only if info is there)
13(a) extension to date: ☐ concurrently filed ☐ not needed ☐ previously filed

14. ☐: Prior application is assigned to _____

by Assignment recorded _____ Reel _____ Frame _____

15. ☐ Attached:

16. This application is made by the following named inventor(s) **(Double check instructions for accuracy):**

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(include Zip Code)			

17. NOTE: FOR ADDITIONAL INVENTORS, check box ☐
and attach sheet with same information regarding additional inventors.

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08/786937

APPLICATION UNDER UNITED STATES PATENT LAWS

Invention: LHRH-Antagonists in the Treatment of Fertility Disorders

Inventor (s): Bouchard, Philippe
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Devroey, Paul
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This is a:

- ☐ Provisional Application
- ☒ Regular Utility Application
- ☐ Continuing Application
- ☐ PCT National Phase Application
- ☐ Design Application
- ☐ Reissue Application
- ☐ Plant Application

SPECIFICATION